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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,818	07/19/2006	Marie Dutreix	BJS-3665-177	2272

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,818	DUTREIX ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-30 and 32-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-30 and 32-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/6/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

A new form 892 that includes the Klem reference is attached to this action. The Opalinska reference is not included on this form because it has not been cited in an office action; its presence in the IFW file is a mistake.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This claim as amended recites that the claimed molecule comprises a polyethylene glycol chain and "a native oligonucleotide, when used in the loop of an hairpin fragment, preferably a tetradeoxythymidylate." The use of the phrase "preferably" in the claim renders it indefinite because it is unknown if tetradeoxythymidylate is limiting or is merely exemplary. Further, it is unclear if this limitation is meant to define the native oligonucleotide only when the molecule is a hairpin. For the purposes of examination tetradeoxythymidylate is interpreted to be

required only if a hairpin is present. In the absence of a hairpin, the native oligonucleotide is interpreted as comprising at least two unmodified nucleotides, thus claim 29 is interpreted to require a polyethylene glycol or substituted or unsubstituted hydrocarbon chain and a native oligonucleotide of at least two unmodified nucleotides.

Claim Rejections - 35 USC § 103

Claims 17-30 and 32-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Omori (DNA repair 2002, of record) in view of Marthinet et al. (Gene Therapy 2000, of record) and Klem (US 2003/0176376, of record).

The claims are directed to methods of enhancing tumor sensitivity and treating cancer by administering a double stranded nucleic acid of at least 16 bp that is a substrate for a Ku protein involved in the NHEJ pathway in combination with a DNA damaging agent. The nucleic acid can be prior to or along with the additional therapy, can be used to treat several types of cancer and is administered by routes that include direct intratumoral injection. Specific claims recite that the nucleic acid is 16-200 bp, is a linear or a hairpin nucleic acid, the free end is blunt or overhanging, the nucleic acid comprises modified nucleotides such as modified backbones, sugars or nucleobases, and the nucleic acid is synthesized chemically or biologically. The claims further recite that the nucleic acid is capable of being taken up into the cell nucleus and may contain an element such as a hydrocarbon chain that hampers DNA replication or repair.

Omori et al. teach that Ku70 protein is involved in DNA double-strand break repair and Ku70-deficient cells have increased radiosensitivity to ionizing radiation.

Omori et al. use an antisense oligonucleotide targeted to Ku70 to suppress Ku70 protein expression in human squamous cell lung carcinoma cell line. The antisense treated cells were more radio- and chemosensitive than the parental cells. Omori et al. note that because clinical cancer radiotherapy is usually performed in multiple fractions, even a small increase in radiosensitivity at a low dose would yield significant differences in biological effect and suggest that inhibition of Ku70 could be applied therapeutically. Omori et al. do teach the use of double stranded decoy molecules to suppress Ku70.

Marthinet et al. teach on page 1225, first column that antisense oligonucleotides are a known strategy to modify expression of genes responsible for malignancy and resistance to therapy. Marthinet et al. further teach that double-stranded oligodeoxynucleotides designed to reproduce regulatory *cis*-elements have been used in a new class of anti-gene strategy and have been successfully applied to several diseases. Marthinet et al. teach the use of both antisense oligonucleotides and double stranded decoy oligonucleotides to block expression of the MDR phenotype in cancer cells. The teachings of Marthinet et al. demonstrate that both antisense and decoy based therapy is effective and provides evidence that the two approaches are equivalent.

At the time the invention was made those of ordinary skill in the art were well aware of the design principles of decoys such as the use of modified nucleotides and that cancer treatment routinely involves combination of nucleic acid therapies with other chemotherapeutic agents. Klem exemplifies these concepts; teaching that cancer treatment with decoy oligomers can be performed with other therapies, defined at

paragraph 29 as including radiation therapy. Klem further teaches at paragraphs 56-64 that decoys can comprise modified nucleotides, including modified backbone moieties such as phosphorothioate and methylphosphonate, are generally at least 16 bases in length and can comprise linkers as shown in table 1 which can be non-nucleotide linkers. Linkers are further defined at paragraph 80 as including hydrocarbon and polyethylene glycol chains. Klem further teaches that these agents can be administered by a variety of routes.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a decoy molecule targeted to a Ku protein to enhance tumor sensitivity or treat cancer by administration in combination with another cancer therapy. Omori et al. provide a reason to target proteins involved in double strand break repair by teaching that inhibition of Ku70 increases radiation sensitivity of tumor cells and suggest this is a viable therapeutic target. Based on the teachings of Marthinet et al. and Klem, one of ordinary skill in the art would recognize that decoy oligomers are an equivalent agent to the antisense oligonucleotides used by Omori et al. and that the use of one over the other is simple substitution of one known element for another. Based on the teachings of Klem of how to make decoys, administer them and combine them with other cancer therapies, one of ordinary skill in the art would be motivated and have a reasonable expectation of success in making decoys with these characteristics and using them therapeutically. Because these decoys meet the structural limitations of the claims they are assumed in the absence of evidence to the contrary to provide the functions recited in claim 22. Based on the teachings of Klem of decoys comprising

modified nucleotides and non-nucleotide moieties at the termini or internally, one of ordinary skill in the art would be motivated and have a reasonable expectation of success in incorporating such moieties into a decoy that binds to Ku70.

Thus, the invention of claims 17-30 and 32-38 would have been obvious, as a whole, at the time the invention was made.

Response to Arguments

Applicants traverse the 103 rejection by arguing that the decoys used by Marthinet and Klem are transcriptional decoys and that the goal of this strategy, trapping of transcription factors with specific sequences, is different from the goal instant invention: rendering Ku protein unavailable to participate in double strand break repair of DNA. Applicants note that the decoys of the invention do not modify the Ku gene and protein expression as suggested by Omori et al, and because they act independently of sequence do not need to have homology with the regulatory element of the gene encoding Ku protein.

These arguments are not persuasive because although many of the decoys known in the art, such as those cited in the rejection, are targeted to transcription factors, those of ordinary skill are aware that the basis of their mechanism of action is the blocking of the protein's binding site. It is correct that for proteins that bind a specific sequence the sequence would be a design consideration when making a decoy, but because decoys are known act via this blocking effect, those of ordinary skill in the art will immediately recognize that decoys can be used against any protein that

binds nucleic acids and that any sequence requirements, or even sequence independence, can be easily factored into the design of any decoy. Further, while applicants argue that the molecules of the do not need to have homology with the regulatory element of the gene encoding Ku protein, it is noted that the claims do not prohibit such homology; requiring only that the nucleic acid be a substrate for binding by Ku70. As applicants note, this binding is independent of sequence, therefore any sequence can be used.

Applicants further argue the teachings of Marthinet et al. and Klem et al. are not suggestive of targeting Ku70 because the transcriptional decoy strategy requires the presence of specific transcriptional elements to be targeted. Applicants point to portions of Marthinet et al. emphasizing that this reference emphasizes the target specificity of their decoy teachings.

This is unpersuasive because these references are not relied on for a teaching of how to target Ku70, but to demonstrate that the use of double stranded decoys is known to those of ordinary skill and has been used therapeutically.

Applicants argue that none of the cited documents teach specific transcriptional elements that can be used in the transcriptional decoy strategy to specifically decrease the expression of Ku70 and that the references would not be combined because of the lack of such teaching.

This is unpersuasive because the claims do not require that the nucleic acid agent have any particular sequence, in fact applicants themselves state that blocking of

Ku70 activity is independent of sequence, so a teaching of transcriptional elements that specifically decrease the expression of Ku70 would be unnecessary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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